

University of Dundee

A pragmatic approach to simplifying inhaler therapy for COPD

Lipworth, Brian; Jabbal, Sunny

Published in:
The Lancet Respiratory Medicine

DOI:
[10.1016/S2213-2600\(17\)30264-3](https://doi.org/10.1016/S2213-2600(17)30264-3)

Publication date:
2017

Licence:
CC BY-NC-ND

Document Version
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

Citation for published version (APA):

Lipworth, B., & Jabbal, S. (2017). A pragmatic approach to simplifying inhaler therapy for COPD. *The Lancet Respiratory Medicine*, 5(9), 679-681. [https://doi.org/10.1016/S2213-2600\(17\)30264-3](https://doi.org/10.1016/S2213-2600(17)30264-3)

General rights

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

A pragmatic approach to simplifying inhaler therapy for COPD

Dr Brian Lipworth & Dr Sunny Jabbal

Scottish Centre for Respiratory Research

School of Medicine

University of Dundee

Ninewells Hospital

Dundee, DD1 9SY

Correspondence: b.j.lipworth@dundee.ac.uk Tel: +44 (0)1382 383188, Fax: +44 (0)1382 383259

Word count = 786

Conflict of interest

BL reports grants and personal fees from Chiesi, Meda and Teva, personal fees from Boehringer Ingelheim, grants from Janssen, grants from AstraZeneca, grants from Roche, grants from Chiesi, grants from Sanofi outside the submitted work, BL's son is an employee of Boehringer Ingelheim. SJ reports personal fees from Pfizer, personal fees and non-financial support from Chiesi Pharma and Astra Zeneca, non-financial support and other from Napp outside the submitted work.

Current guidelines for COPD recommend a stepwise approach to inhaled pharmacotherapy.¹ The assessment of COPD is based on severity of airflow limitation (spirometric grades 1-4) as well as symptom burden and exacerbation risk (groups A-D). Symptoms and exacerbations are the main drivers of treatment. The greatest health care burden is associated with frequent exacerbations of COPD – i.e. those patients in groups C and D.

The guidelines are rather complicated suggesting moving up the treatment escalator from monotherapy with long acting beta-agonist (LABA) or long acting muscarinic antagonist (LAMA) to combination inhaler therapy with LABA/LAMA or inhaled corticosteroid (ICS) with LABA (ICS/LABA) and then triple therapy with ICS/LABA/LAMA. Currently, triple therapy requires the use of two separate inhalers comprising ICS/LABA and LAMA often via different devices, which in turn may be associated with poorer long term compliance. However single triple therapy inhalers currently in development may soon become available including once daily with fluticasone furoate/vilanterol/umeclidinium, or twice daily with beclometasone/formoterol/glycopyrronium or budesonide/formoterol/glycopyrronium. Given that there are already numerous different inhaler devices for mono and dual therapy, prescribers are understandably becoming increasingly confused especially in primary care.

We therefore propose a less complex and more pragmatic approach to prescribing stratified by exacerbations and eosinophils, whereby there are only two options for patients with COPD, namely single inhalers comprising either LABA/LAMA or ICS/LABA/LAMA (Figure). The rationale for this simplified approach is proposed as follows. Using two long acting bronchodilators is more effective than one in terms of lung function, symptoms and exacerbations.² Hence it would appear cogent to use a LABA/LAMA single inhaler combination as the starting point for patients with increased symptoms or more frequent exacerbations. This is also supported by evidence from real life prescribing data where patients often step up from monotherapy to combination therapy, presumably because the latter results in better control.³ Hence initiating treatment with LABA/LAMA will result in fewer treatment failures than monotherapy, in turn improving the likelihood of patients adhering to their prescribed inhalers along with a lower health care burden.

The use of ICS/LABA has been shown to be more effective in reducing exacerbations in patients with an eosinophilic component to their COPD.^{4,5} Moreover patients with COPD who have frequent exacerbations in conjunction with blood eosinophilia (>300 cells/ul) are at higher risk of exacerbating when stepping down from triple therapy upon subsequent withdrawal of ICS.^{6,7}

The situation with regards to ICS/LABA is further complicated by the results of the FLAME study⁸ which found overall that once daily indacaterol/glycopyrronium was superior to twice daily fluticasone/salmeterol for effects on exacerbations, lung function and quality of life. However in a subsequent post hoc analysis of FLAME it was found that LABA/LAMA was no better than ICS/LABA on exacerbations in patients with blood eosinophils >300 cells/ul.⁹ Triple therapy via a single or separate inhalers containing ICS/LABA/LAMA has been shown to be superior to ICS/LABA on lung function, quality of life and exacerbations.¹⁰⁻¹² Given the greater benefits of ICS on exacerbations in patients with eosinophilic COPD, there would appear to be a rationale for starting off with triple therapy for individuals with a higher exacerbation risk, without going through the first step of ICS/LABA, especially once the single triple inhalers become available. Pointedly there are at present no head to head comparisons of triple therapy versus LABA/LAMA. However one might expect that triple therapy would be superior to LABA/LAMA but only for effects on exacerbations in patients with eosinophilic COPD with frequent exacerbations. Whether triple therapy should also be considered as step up for non-eosinophilic patients who are exacerbating despite LABA/LAMA remains unclear, especially in view of the pneumonia risk associated with ICS use.

Where does this all leave us moving forwards with regards to simplifying inhaled therapy for COPD especially for those patients in groups C and D with frequent exacerbations? We would suggest a pragmatic approach using single inhaler therapy whereby patients with eosinophilic COPD (i.e. >300 cells/ul) receive ICS/LABA/LABA and those with non-eosinophilic COPD (i.e. <300 cells/ul) receive LABA/LAMA (Figure). For patients in group B the starting point irrespective of eosinophils would be LABA/LAMA since these patients

have more symptoms but infrequent exacerbations and therefore do not need the ICS moiety. We would advocate two blood draws if necessary to identify those patients with eosinophilic COPD. The most suitable inhaler device for an individual patient is the one which they feel comfortable with, can use correctly and will take on a regular basis in the long term. Real life studies are now indicated to test this hypothesis in COPD patients stratified according to exacerbation frequency and blood eosinophils. Such pragmatic studies should also assess whether using a once or twice daily dosing single inhaler regimen is the best way forward.

Figure Legend

Pragmatic approach to using dual (LABA/LAMA) or triple (ICS/LABA/LAMA) single inhaler therapy for COPD stratified according to blood eosinophils (low <300 cells/ul or high >300 cells/ul) and exacerbation risk. The interrupted line between dual and triple therapy indicates the possibility of stepping up or down.

References

1. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. *Am J Respir Crit Care Med* 2017; **195**(5): 557-82.
2. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med* 2013; **1**(3): 199-209.
3. Edwards SC, Fairbrother SE, Scowcroft A, Chiu G, Ternouth A, Lipworth BJ. The burden of chronic obstructive pulmonary disease associated with maintenance monotherapy in the UK. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 2851-8.
4. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015; **3**(6): 435-42.
5. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; **192**(4): 523-5.
6. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; **4**(5): 390-8.
7. Calverley PM, Tetzlaff K, Vogelmeier C, et al. Eosinophilia, Frequent Exacerbations, and Steroid Response in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017. Published on 17-March-2017 as 10.1164/rccm.201612-2525LE
8. Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med* 2016; **374**(23): 2222-34.

9. Roche N, Chapman KR, Vogelmeier CF, et al. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *Am J Respir Crit Care Med* 2017; **195**(9): 1189-97.
10. Lipson DA, Barnacle H, Birk R, et al. FULFIL Trial: Once-Daily Triple Therapy in Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017.
11. Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; **388**(10048): 963-73.
12. Short PM, Williamson PA, Elder DH, Lipworth SI, Schembri S, Lipworth BJ. The impact of tiotropium on mortality and exacerbations when added to inhaled corticosteroids and long-acting beta-agonist therapy in COPD. *Chest* 2012; **141**(1): 81-6.